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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,569	07/16/2002	Takashi Muramatsu	SPO-116	7190

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,569	MURAMATSU ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 13, 2004 has been entered.

2. Claims 1-16 are pending.

Claims 10-12, drawn to non-elected inventions are withdrawn from examination.

Claims 1, 9, 13, 15 and 16 have been amended.

Claims 1-9 and 13-16 are examined on the merits.

Oath/Declaration

3. The declaration under 37 CFR 1.132 submitted December 13, 2004 has been reviewed by the Examiner.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

4. The rejection of claims 13-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of

Applicants' amendments to the claims, arguments and a listing of citations described within the specification by specific pages and line numbers providing support, see page 6 of the Remarks submitted December 13, 2004.

5. The rejection of claims 1-9 and 13-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' amendments and arguments presented in the claims and Remarks, pages 10-12.

Claim Rejections - 35 USC § 102

6. The rejection of claims 1 and 9 under 35 U.S.C. 102(b) as being anticipated by Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9) is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 103

7. The rejection of claims 1-8, 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over Song et al. (Biomedical Research 18(5): 375-381, 1997) is withdrawn.

Claim Rejections - 35 USC § 103

8. The rejection of claims 1, 9 and 13 under 35 U.S.C. 103(a) as being unpatentable over Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9) is withdrawn in light of Applicants' claim amendments.

Maintained Rejections and New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. The rejection of claims 1-9 and 13-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Applicants assert that human midkine is known in the art and "...[their] specification clearly sets forth the distinguishing identifying characteristics needed to identify members of the 'genus'", see page 8, first full paragraph of Remarks. Applicants assert the claim amendments do not embody fragments and mutants as listed within the specification, see bridging paragraph of pages 8 and 9 of the Remarks. In conclusion, Applicants assert "...[they] have clearly set forth the distinguishing identifying characteristics needed to identify members of the 'genus', the limited species disclosed are sufficient to demonstrate possession thereof.", see bridging paragraph of pages 8 and 9 in the Remarks.

Applicants have amended the claims to include the recitation "human midkine in a body fluid", however this does not preclude the instant rejection. The claims are not read in a vacuum and are given the broadest and most

reasonable interpretation. The recitation, midkine supported by the specification clearly notes that midkine includes not only a full-length MK protein, a fragment comprising an amino acid sequence of any length and mutants, see bridging paragraph of pages 4 and 5. The term, midkine embraces all of the listed variants. Furthermore, the biological activities noted in the specification are not limited to any specific activities. Applicants suggest midkine activities not only include physiological action of midkine cells and immunological reactivity with an anti-MK antibody, see bridging paragraph of pages 4 and 5. These listed activities do not provide sufficient distinguishing identifying characteristics needed to identify members of the genus as suggested by Applicants. There is no nexus established by Applicants or listed in the specification between structure and function. There is insufficient guidance provided establishing a core structure that all midkine molecules must have that is critical to its function and the specification does not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identifiy members of the genus the rejection is maintained. One of ordinary skill in the art would not conclude that Applicants were in possession of all midkine molecules, i.e. mutants and molecules of arbitrary length. The claims thus encompass midkine molecules that vary widely in structure and function. For the reasons of record and set forth the rejection is maintained.

10. The rejection of claims 1-9 and 13-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting cancer and assessing cancer prognosis comprising the steps of measuring the level of human full-length and wild type midkine protein in a biological sample, does not reasonably provide enablement for a method for detecting cancer and assessing cancer prognosis comprising the measuring the level of a midkine mutant or a midkine fragment is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue that the amendments to the claims render the instant enablement rejection moot. Applicants assert the claims are narrowly tailored to "human midkine in a body fluid"., see bridging paragraph of pages 9 and 10 of the Remarks. These points of view have been fully considered but found unpersuasive.

Applicants are reminded that the claims and disclosures are not to be evaluated in a vacuum and the Office gives claims their broadest reasonable interpretation in light of the supporting disclosure. The term midkine embraces not only full-length MK protein, but also mutants and variant proteins, see bridging paragraph of pages 4 and 5. Applicants' examples seem to exemplify Applicants use of an antibody that recognized human full-length MK (not defined by an amino acid sequence or sequence identifier) and not mutants and arbitrary fragments of MK. The specification does not provide enabling disclosure that

evidences a method for detecting cancer comprising measuring a midkine mutant lacking a domain near the N terminus, which is ultimately a fragment of MK, implementing the said method with an antibody that recognizes the said mutant or a method of assessing cancer prognosis using the said fragments and undefined mutant and variant MK molecules before and after treatment. The specification nor Remarks provide sufficient guidance as to which of the amino acids may be changed in mutant MK of arbitrary amino acid length while MK structural or functional activity and specificity is retained. Without such guidance, the changes, which can be made in the MK amino acids, still maintain biological activity or structural specificity of MK molecules by MK antibodies is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejections - 35 USC § 102

11. The rejection of claims 1-9, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Song et al. (Biomedical Research 18(5): 375-381, 1997) is maintained and made.

Applicants assert "the present method constitutes a revolutionary first screening" and the claims have been amended to reflect such, see bridging paragraph of pages 12 and 13. Applicants argue "...Song does not explicitly mention 'early cancer' or indicate the stage of the cancers assayed.", see bridging paragraph of pages 13 and 14 or Remarks. Applicants submitted a declaration by Dr. Kenji on September 9, 2004 notes that a cancer that has not metastasized is not necessarily an "early cancer" and conversely a cancer that has metastasized is not necessarily an advanced cancer. Applicants also discuss the criteria of inherency and conclude "Song...[does not] disclose or suggest a linear relationship between level of midkine and a particular prognosis or cancer stage", see first sentence listed on page 15 of Remarks. These arguments and points of view have been considered but found unpersuasive.

Song discloses a method for measuring a human midkine (MK) protein in sera from patients with early stage gastric and lung cancer, see pages 376-378. It is reasonable to regard these cancers as early stage cancers as defined by Applicants (see Appendix I and page 4, lines 18-30) because as noted in the Table found on page 376 of Song these cancers have no lymph node metastasis, which is a reflection of being a stage 0 and stage I cancer. Absent evidence to the contrary Song continues to read on Applicants' claimed method. Normal human serum MK was compared with the MK level of the cancer patients, see page 375, column 2, section before Materials and Methods section. Detection and measure of MK was conducted with an enzyme-linked immunoassay using a pair of antibodies, see page 375, column 2, Materials and Methods section.

Song continues to anticipate the claimed invention with particularity the claims limited to hepatocellular carcinoma because Applicants' claim 1, part b implicitly notes, "wherein an elevated measured level as compared to the control indicates the presence of early cancer", see lines 7 and 8. In essence the claims read on methods absolute in the contrast of elevated midkine within samples compared to the control, which is within the scope of the claims. Song lists " [u]sing this assay, normal human serum was shown to contain undetectable or low levels of MK, whereas the majority of cases of hepatocellular carcinoma the serum MK level was markedly increased.", see page 375, column 2, paragraph above the Materials... section. Essentially, Song's method was conducted with early cancer patients given the description established in the claims. This disclosure reads on Applicants claims.

Given the broadest interpretation it is reasonable to conclude that "treatment" encompasses surgery. Song discloses MK level measurement before and after treatment, see page 377, column 2, Serum MK section; and page 378, Figure 1.

12. The rejection of claims 1, 4, 5, 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12) is maintained.

Applicants argue "the Examiner admits...Muramatsu does not explicitly mention "early cancer" or indicate the stage of the cancers assayed. ", see Remarks page 16. Applicants also declare "...there is no direct relationship between a cancer not metastasizing to the lymph nodes and/or distant organs" and "...Applicants' claimed invention...is neither expressly nor inherently disclosed or suggested by the Muramatsu reference.", see Remarks, page 17, third sentence and page 18, first full paragraph. These arguments, the declaration and points of view have been considered, but found unpersuasive.

Muramatsu continues to anticipate the claimed invention because Applicants' claim 1, part b implicitly notes, "wherein an elevated measured level as compared to the control indicates the presence of early cancer", see lines 7 and 8. In essence the claims read on methods absolute in the contrast of elevated midkine within samples compared to the control, which is within the scope of the claims. Muramatsu observed "[t]he MK levels in sera of normal human subjects were either undetectable or less than 0.6ng/ml...However, in

more than half the hepatocellular carcinoma patients, MK was detectable in sera in the range of 0.6-8 ng/ml.", see page 1173, column 2, Determination... section. Essentially, Muramatsu's method was conducted with early cancer patients given the description established in the claims. This disclosure reads on Applicants claims. Given the endpoint of both methods are the same, comparing the level of human midkine protein between a cancerous sample and control sample Muramatsu continues to anticipates the claims. Muramatsu anticipates the claimed invention for the reasons of record.

Claim Rejections - 35 USC § 103

13. The rejection of claims 1, 4, 5, 8, 9 and 13 under 35 U.S.C. 103(a) as being unpatentable over Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12). The teachings of Muramatsu have been presented and reiterated above. Muramatsu does not teach the anticipated method occurring after treatment and correlating the difference in the measure levels to determine successful therapy and positive prognosis.

Applicants argue " Muramatsu...simply disclose[s] that serum levels of midkine may be elevated...in certain hepatocellular carcinomas" and "[t]here is no disclosure that serum midkine levels directly correlate with cancer progression and prognosis...", see Remarks bridging paragraph of pages 18 and 19. These arguments have been carefully considered but found unpersuasive.

Muramatsu notes "...that the [midkine] level might be correlated with tumor grade", see page 1174, column 1, last sentence of article. As noted in the

102(b) Muramatsu compared the level of human midkine protein between a cancerous sample and control sample thereby anticipating the claims in particularity wherein claim 1, part b reads, "wherein an elevated measured level as compared to the control indicates the presence of early cancer", see lines 7 and 8. Accordingly, It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to implement a comparative analysis before and after a method of cancer treatment because a health practitioner would need to make a determination of whether the mode of treatment was indeed effective. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success to monitor the patient's expression of a tumor marker in determining the effectiveness of the treatment modality in an effort to determine the patient's prognosis, as well as enhancing the ability of a physician to change and/or optimize therapy.

Furthermore, although the claims recite a specific treatment point, no positive recitation of the time restraint distinguishes the claims over the references. Thus, the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she

can normally be reached between the hours of 6:30 am to 5:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
30 May 2005